7/ Translation + Decl

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RAPIDLY DISINTEGRABLE SOLID PREPARATION

DECLARATION

I, kyoko YOSHIDA, technical translator, declare that I am a citizen of Japan, residing at c/o Takeda Chemical Industries, Ltd., of 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka, Japan; that I am competent to make English translations and have had considerable experience in that work; that the attached are true translations into the English language of the Japanese Patent Application No. 213049/1998.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 25th day of June, 2002

Kyoko Yoshida

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[Title of the Invention] Rapidly Disintegrable Solid Preparation

[Claims]

[Claim 1] A rapidly disintegrable solid preparation which comprises (i) a pharmaceutical ingredient, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group.

[Claim 2] A preparation of Claim 1, which is an orally rapidly disintegrable solid preparation.

[Claim 3] A preparation of Claim 1, wherein the sugar is a sugar alcohol.

[Claim 4] A preparation of Claim 3, wherein the sugar alcohol is mannitol or erythritol.

[Claim 5] A preparation of Claim 1, wherein the sugar is in an amount of 5 to 97 parts by weight per 100 parts by weight of the solid preparation.

[Claim 6] A preparation of Claim 1, wherein the low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group is used in an amount of 3 to 50 parts by weight per 100 parts by weight of the solid preparation.

[Claim 7] A preparation of Claim 1, which is a tablet.

[Claim 8] A preparation of Claim 1, wherein the pharmaceutical ingredient is lansoprazole.

[Claim 9] A preparation of Claim 1, wherein the pharmaceutical ingredient is voglibose.

[Claim 10] A preparation of Claim 1, wherein the pharmaceutical ingredient is manidipine hydrochloride.

[Claim 11] Use of a low-substituted hydroxypropylcellulose having 5 % by weight or

more to less than 7 % by weight of hydroxypropoxyl group for producing a rapidly disintegrable solid preparation comprising a pharmaceutical ingredient and a sugar.

[Claim 12] A method for improving fast disintegrability of a solid preparation comprising a pharmaceutical ingredient and a sugar which is characterized in that a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group is contained therein.

[Detailed Description of the Invention]

[0001]

[Technical Field to which the Invention belongs]

The present invention relates to a solid preparation having fast disintegrability in the existence of saliva in the oral cavity or a little water, particularly a rapidly disintegrable solid preparation which is usable as an orally disintegrable solid preparation.

[0002]

[Background Art]

It has been desired to develop an orally disintegrable solid preparation which can be easily administered to elders or children without water. As background arts which disclose such a preparation, for example, there are following background arts.

JP-A-9-48726 discloses an orally rapidly disintegrable preparation comprising a drug and a material which is produced by wetting in a moldable way on humidifying and is retaining a shape after molding and drying. As such materials, a sugar, sugar alcohol and a water-soluble polymer material are exemplified.

JP-A-9-71523 discloses a tablet containing a drug, crystalline cellulose, a low-substituted hydroxypropylcellulose and a lubricant and having fast disintegrability in the oral cavity.

EP-A 839526 discloses a solid pharmaceutical preparation containing a pharmaceutical ingredient, erythritol, crystalline cellulose and a disintegrator.

However, these background arts have not described (i) a pharmaceutical ingredient, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group of the present invention.

[0003]

[Problems that the Invention is to solve]

There has been desired the development of a rapidly disintegrable solid preparation having fast disintegrability in the existence of saliva in the oral cavity or a little water, having suitable strength (hardness) so that it may not be damaged through production processes and distribution, and further having no roughness.

[0004]

[Means to solve the Problems]

The present invention relates to:

(1) a rapidly disintegrable solid preparation which comprises (i) a pharmaceutical ingredient, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group;

(2) a preparation of the above (1), which is an orally rapidly disintegrable solid preparation;

(3) a preparation of the above (1), wherein the sugar is a sugar alcohol;

(4) a preparation of the above (3), wherein the sugar alcohol is mannitol or erythritol;

(5) a preparation of the above (1), wherein the sugar is in an amount of 5 to 97 parts by weight per 100 parts by weight of the solid preparation;

(6) a preparation of the above (1), wherein the low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group is used in an amount of 3 to 50 parts by weight per 100 parts by weight of the solid preparation;

(7) a preparation of the above (1), which is a tablet;

(8) a preparation of the above (1), wherein the pharmaceutical ingredient is lansoprazole;

(9) a preparation of the above (1), wherein the pharmaceutical ingredient is voglibose;

(10) a preparation of the above (1), wherein the pharmaceutical ingredient is manidipine hydrochloride;

(11) use of a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group for producing a rapidly disintegrable solid preparation comprising a pharmaceutical ingredient and a sugar; and

(12) a method for improving fast disintegrability of a solid preparation comprising a pharmaceutical ingredient and a sugar which is characterized in that a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group is contained therein.

[0005]

The pharmaceutical ingredient used in the present invention are in any condition such as solid, powdery, crystalline, oily and solution conditions. As such pharmaceutical ingredient, for example, one or more ingredient(s) selected from the group comprising nourishing and cordial agents, antipyretic-anodyne-anti-inflammatory drugs, psychotropic drugs, antianxiety drugs, antidepressants, hypnotic-sedative drugs, spasmolytics, central nervous system drugs, brain metabolism ameliorating agents,

antiepileptics, sympathomimetics, gastrointestinal agents, antacids, antiulcer agents, antitussive-expetorants, antiemetics, respiratory accelerators, bronchodilators, antiallergic drugs, dental buccal drugs, antihistamines, cardiotonics, antiarrythmic drugs, diuretics, antihypertensive agents, vasoconstrictors, coronary vasodilators, peripheral vasodilators, antihypolipidemic agents, cholagogues, antibiotics, chemotherapeutic drugs, antidiabetic agents, drugs for osteoporosis, skeletal muscle relaxants, antivertigos, hormones, alkaloid narcotics, sulfa drugs, arthrifuges, blood coagulation inhibitors, antitumor agents, drugs for Alzheimer's disease and the like is/are exemplified.

[0006]

As the nourishing and cordial agents, for instance, vitamins such as vitamin A, vitamin D, vitamin E (such as d-α-tocopherol acetate and the like), vitamin B_1 (such as dibenzoylthiamine, fursultiamine hydrochloride and the like), vitamin B_2 (such as riboflavin butyrate and the like), vitamin B_6 (such as pyridoxine hydrochloride and the like), vitamin C (such as ascorbic acid, sodium L-ascorbate and the like) and vitamin B_{12} (such as hydroxocobalamin acetate and the like); minerals such as calcium, magnesium, iron and the like; proteins, amino acids, oligosaccharides, crude drugs and the like are exemplified.

As the antipyretic-anodyne-antiinflammatory drugs, for instance, aspirin, acetaminophen, ethenzamide, ibuprofen, diphenhydramine hydrochloride, dl-chlorpheniramine maleate, dihydrocodeine phosphate, noscapine, methylephedrine hydrochloride, phenylpropanolamine hydrochloride, caffeine, anhydrous caffein, serrapeptase, lysozyme chloride, tolfenamic acid, mefenamic acid, sodium diclofenac, flufenamic acid, salicylamide, aminopyrine, ketoprofen, indometacin, bucolome, pentazocine and the like are exemplified.

As the antipsychotic drugs, for instance, chlorpromazine, reserpine and the like

are exemplified.

As the antianxiety drugs, for instance, alprazolam, chlordiazepoxide, diazepam and the like are exemplified.

As the antidepressants, for instance, imipramine, maprotiline, amphetamine and the like are exemplified.

[0007]

As the hypnotic-sedative drugs, for instance, estazolam, nitrazepam, diazepam, perlapine, sodium phenobarbital and the like are exemplified.

As the spasmolytics, for instance, scopolamine hydrobromide, diphenhydramine hydrochloride, papaverine hydrochloride and the like are exemplified.

As the central nervous system drugs, for instance, citicoline, ROCHIRENIN and the like are exemplified.

As the brain metabolism ameliorating agents, for instance, vinpocetine, meclofenoxate hydrochloride and the like are exemplified.

As the antiepileptics, for instance, phenytoin, carbamazepine and the like are exemplified.

As the sympathomimetics, for instance, isoproterenol hydrochloride and the like are exemplified.

As the gastrointestinal agents, for instance, stomachic-digestives such as diastase, saccharated pepsin, scopolia extract, cellulase AP3, lipase AP and cinnamon oil; intestinal function controlling agents such as berberine chloride, resistant lactic acid bacterium, Lactobacillus bifidus and the like are exemplified.

As the antacids, for instance, magnesium carbonate, sodium hydrogencarbonate, magnesium aluminometasilicate, synthetic hydrotalcite, precipitated calcium carbonate, magnesium oxide and the like are exemplified.

As the antiulcer agents, for instance, lansoprazole, omeprazole, rabeprazole, pantoprazole, famotidine, cimetidine, ranitidine hydrochloride and the like are exemplified.

[0008]

As the antitussive-expetorants, for instance, chloperastine hydrochloride, dextromethorphan hydrobromide, theophylline, potassium guaiacolsulfonate, guaiafenesin, codeine phosphate and the like are exemplified.

As the antiemetics, for instance, difenidol hydrochloride, metoclopramide and the like are exemplified.

As the respiratory accelerators, for instance, levallorphan tartrate and the like are exemplified.

As the bronchodilators, for instance, theophylline, salbutanol sulfate and the like are exemplified.

As the antiallergic drugs, for instance, amlexanox, seratrodast and the like are exemplified.

As the dental buccal drugs, for instance, oxytetracycline, triamcinolone acetonide, chlorhexidine hydrochloride, lidocaine and the like are exemplified.

As the antihistamines, for instance, diphenhydramine hydrochloride, promethazine, isothipendyl hydrochloride, dl-chlorpheniramine maleate and the like are exemplified.

As the cardiotonics, for instance, caffeine, digoxin and the like are exemplified.

As the antiarrythmic drugs, for instance, procainamide hydrochloride, propranolol hydrochloride, pindolol and the like are exemplified.

As the diuretics, for instance, isosorbide, furosemide and the like are exemplified.

As the antihypertensive agents, for instance, delapril hydrochloride, captopril, hexamethonium bromide, hydrazine hydrochloride, labetalol hydrochloride, manidipine hydrochloride, candesartan cilexetil, methyldopa, losartan, valsartan, eprosartan, irbesartan, tasosartan, telmisartan, pomisartan, ripisartan, FORASARUTAN and the like are exemplified.

[0009]

As the vasoconstrictors, for instance, phenylephrine hydrochloride and the like are exemplified.

As the coronary vasodilators, for instance, carbocromen hydrochloride, molsidomine, verapamil hydrochloride and the like are exemplified.

As the peripheral vasodilators, for instance, cinnarizine and the like are exemplified.

As the antihypolipidemic agents, for instance, sodium cerivastatin, simvastatin, sodium pravastatin and the like are exemplified.

As the cholagogues, for instance, dehydrocholic acid, trepibutone and the like are exemplified.

As the antibiotics, for instance, cephems such as cefalexin, amoxicillin, pivmecillinam hydrochloride, cefotiam dihydrochloride, cefozopran hydrochloride, cefmenoxime hemihydrochloride, sodium cefsulodin; synthetic antibacterial agents such as ampicillin, ciclacillin, sodium sulbenicillin, nalidixic acid and enoxacin; monobactams such as carumonam sodium; penems; carbapenems and the like are exemplified.

As the chemotherapeutic drugs, for instance, sulfamethizole hydrochloride, thiazosulfone and the like are exemplified.

As the antidiabetic agents, for instance, tolbutamide, voglibose,

(hydrochloride)pioglitazone, troglitazone, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (BRL-49653), acarbose, miglitol, emigitate and the like are exemplified.

As the drugs for osteoporosis, for instance, ipriflavone and the like are exemplified.

As the skeletal muscle relaxants, for instance, methocarbamol and the like are exemplified.

As the antivertigos, for instance, meclizine hydrochloride, dimenhydrinate and the like are exemplified.

[0010]

As the hormones, for instance, sodium liothyronine, sodium dexamethasone phosphate, prednisolone, oxendolone, leuprorelin acetate and the like are exemplified.

As the alkaloid narcotics, for instance, opium, morphine hydrochloride, ipecac, oxycodone hydrochloride, opium alkaloids hydrochlorides, cocaine hydrochloride and the like are exemplified.

As the sulfa drugs, for instance, sulfamine, sulfamethizole and the like are exemplified.

As the arthrifuges, for instance, allopurinol, colchicine and the like are exemplified.

As the blood coagulation inhibitors, for instance, dicoumarol and the like are exemplified.

As the antitumor agents, for instance, 5-fluorouracil, uracil, mitomycin and the like are exemplified.

As the drugs for Alzheimer's disease, for instance, idebenone, vinpocetine and the like are exemplified.

[0011]

The above pharmaceutical ingredient is used in an amount of, for example, 0.01 to 70 parts by weight, preferably 0.02 to 50 parts by weight, more preferably 0.05 to 30 parts by weight, per 100 parts by weight of the solid preparation.

Among the above pharmaceutical ingredients, nourishing and cordial agents, antipyretic-anodyne-antiinflammatory drugs, hypnotic-sedative drugs, central nervous system drugs, gastrointestinal agents, antiulcer agents, antitussive-expetorants, antiallergic drugs, antiarrhythmic drugs, diuretics, antihypertensive agents, vasoconstrictors, coronary vasodilators, antihypolipidemic agents, antidiabetic agents, drugs for osteoporosis, skeletal muscle relaxants, antivertigos and the like are preferably used.

In the present invention, the pharmaceutical ingredients preferably used are antiulcer agents such as lansoprazole; antidiabetic agents such as voglibose; and antihypertensive agents such as manidipine hydrochloride and candesartan cilexetil and the like are exemplified.

[0012]

As the sugars used in the present invention, for example, sugar, starch sugar, lactose, honey and sugar alcohol are exemplified. Such sugars are optionally used in an admixture thereof with suitable ratio.

As the sugar, for example, sucrose, coupling sugar, fructo-oligosaccharide, palatinose are exemplified.

As the starch sugar, for example, glucose, maltose, powdered sugar, starch syrup, fructose and the like are exemplified.

As the lactose, for example, lactose, isomerized lactose (lactulose), reduced lactose (lactitol) and the like are exemplified.

As the honey, various kinds of honey which are generally edible are exemplified.

As the sugar alcohol, for example, mannitol, erythritol, sorbitol, maltitol, reduced starch saccharide, xylitol, reduced paratinose and the like are exemplified. In this case, erythritol which is produced by fermentation using glucose as a starting material with yeast in general and has at most 50 mesh of the particle size is usually used. Such erythritol is commercially available [for example, from Nikken Chemicals Co., Ltd.].

The above sugars are preferably water-soluble sugars. The water-soluble sugars mean any water-soluble sugars which need at most 30 ml of water when 1 g of sugar is added into water and then dissolved within about 30 minutes at 20°C by strongly shaking every 5 minutes for 30 seconds.

In the present invention, the sugar is preferably the sugar alcohol, more preferably mannitol or erythritol.

The sugar is used in an amount of 5 to 97 parts by weight, preferably 10 to 90 parts by weight, per 100 parts by weight of the solid preparation. If the amount of the sugar to be used is too much compared with such ranges, sufficient strength of the preparation cannot be obtained. On the contrary, if the amount of the sugar to be used is too small, sufficient fast disintegrability cannot be obtained.

[0013]

The "low-substituted hydroxypropylcellulose having 5 % by weight or more to 7 % by weight of hydroxypropoxyl group" used in the present invention can be produced in accordance with well-known methods, for example, methods described in JP-B-57-53100 or its analogous methods thereof.

At first, alkaline cellulose containing free alkaline and propylene oxide are

reacted to obtain the crude low-substituted hydroxypropylcellulose containing free alkaline.

Concretely, for example, raw material pulp such as wood pulp and cotton leader is immersed in 10 to 50 % concentration of aqueous solution of sodium hydroxide, and pressed to obtain the alkaline cellulose of which NaOH/cellulose ratio is about 0.1 to 1.2 (ratio by weight). Next, the crude low-substituted hydroxypropylcellulose containing free alkaline is obtained by reacting the resulting alkaline cellulose and propylene oxide with stirring at 20 to 90°C for 2 to 8 hours. Propylene oxide is used in an amount so that the content of hydroxypropoxyl group in the desired low-substituted hydroxypropylcellulose can be 5 or more % by weight to 7 % by weight.

The crude low-substituted hydroxypropylcellulose containing free alkaline is dispersed in water or hot water containing 5 to 80 % of acid which is need to neutralize the all amount of alkaline, and a part of the crude low-substituted hydroxypropylcellulose containing free alkaline is dissolved therein. Further, acid is added to neutralize the remained alkaline.

After the neutralization, processes such as drainage, drying and grinding are performed in accordance with the conventional method to obtain the desired low-substituted hydroxypropylcellulose.

[0014]

The particle diameter of "the low-substituted hydroxypropylcellulose having 5 or more to 7 % by weight of hydroxypropoxyl group" (hereinafter, optionally referred to L-HPC) used in the present invention is, for example, 5 to 60 μm as average particle diameter. Preferably, it is 10 to 40 μm as average particle diameter.

In the above ranges, in case that L-HPC having relatively large particle

diameter (for example, L-HPC having 26 to 40 μm of average particle diameter) is used, a pharmaceutical preparation being superior in disintegrability can be produced. On the other hand, in case that L-HPC having relatively small particle diameter (for example, L-HPC having 10 to 25 μm of average particle diameter) is used, the pharmaceutical preparation being superior in strength of the preparation can be produced.

Accordingly, the particle diameter of L-HPC can be suitably selected according to the character of the desired pharmaceutical preparation.

[0015]

The L-HPC in the present invention is used in an amount of 3 to 50 parts by weight, preferably 5 to 40 parts by weight, per 100 parts by weight of the solid preparation. If amount of the L-HPC to be used is too much compared with such ranges, it is not preferable because sufficient disintegrability cannot be obtained. If amount of the L-HPC to be used is too small compared with such ranges, it is not preferable because sufficient strength of the preparation cannot be obtained.

As mentioned above, by using the low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group, it becomes possible to improve fast disintegrability, particularly the orally fast disintegrability, of the solid preparation containing the pharmaceutical ingredient and the sugar.

[0016]

The rapidly disintegrable solid preparation of the present invention is useful particularly as the orally rapidly disintegrable solid preparation and can be administered without water or with water. Further, the rapidly disintegrable solid preparation may be administered after dissolving it with a little water.

As the dosage form of the rapidly disintegrable solid preparation of the present invention, for example, tablet, granule, fine granule and the like are exemplified and tablet is preferable.

[0017]

Unless fast disintegrability (particularly, fast disintegrability in the oral cavity) or strength of the preparation is interfered with, the rapidly disintegrable solid preparation of the present invention may further contain a variety of additives which are commonly used in the manufacture of preparations in general dosage forms. Amount of such additives to be used is one commonly used in the manufacture of preparations in general dosage forms. As such additives, for example, binders, acids, foaming agents, artificial sweeteners, flavorants, lubricants, colorants, stabilizers, disintegrators and the like are exemplified.

Also, when the rapidly disintegrable preparation of the present invention is produced, a fine granular core is optionally used. As such a fine granular core, for example, (1) a spherical granulated product comprising crystalline cellulose and lactose [e.g., a spherical granulated product being about 100 to 200 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) (Nonpareil 105 (trade name), manufactured by Freund Industrial Co., Ltd.), a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (3 parts) and lactose (7 parts) (Nonpareil NP-7:3 (trade name), manufactured by Freund Industrial Co., Ltd., a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose (5 parts) and lactose (5 parts) (Nonpareil NP-5:5 (trade name), manufactured by Freund Industrial Co., Ltd.) and the like], (2) a spherical granulated product being about 150 to 250 μm and comprising crystalline cellulose [avicel SP (trade name), manufactured by Asahi Chemical Industry Co., Ltd. and the like) and the like are

exemplified.

In case that the fine granular core is used, the core is optionally coated with the pharmaceutical ingredient and the above additives, and further coated for masking taste or smell or for imparting enteric dissolubility or sustained-release property by well known methods. As a coating agent in this case, for example, enteric-coated polymers (e.g., cellulose acetate phthalate (CAP), methacrylate copolymer L, methacrylate copolymer LD (Eudragit L30D-55), methacrylate copolymer S, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose and the like), gastric dissolvable polymers (e.g., polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer and the like), water-soluble polymers (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose and the like), slightly soluble-polymers (e.g., ethylcellulose, aminoalkyl methacrylate copolymer RS, ethyl acrylate・methyl methacrylate copolymer and the like), wax and the like are exemplified.

[0018]

As the above binders, for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose, pregelatinized starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan and the like are exemplified. The use of crystalline cellulose as the binder provides the solid preparation which exhibits more excellent strength of the preparation while retaining excellent fast disintegrability in the oral cavity. As the crystalline cellulose, microcrystalline cellulose is also included. As crystalline cellulose, for example, CEOLUS KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-A591 NF (crystalline cellulose・carmellose sodium) and the like are concretely exemplified. Among others, CEOLUS KG 801 referred to highly moldable crystalline cellulose is

preferably used. Such crystalline celluloses are optionally used in an admixture thereof with suitable ratio. Such crystalline celluloses can be commercially available (manufactured by Asahi Chemical Industry Co., Ltd.). The crystalline cellulose is used in an amount of, for example, about 1 to 50 parts by weight, preferably about 2 to 40 parts by weight, more preferably about 2 to 20 parts by weight, per 100 parts by weight of the solid preparation.

[0019]

As the acids, for example, citric acid, tartaric acid, malic acid and the like are exemplified.

As the foaming agents, for example, sodium bicarbonate and the like are exemplified.

As the artificial sweeteners, for example, saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, thaumatin and the like are exemplified.

As the flavorants, for example, lemon, lemon lime, orange, mentnol and the like are exemplified.

As the lubricants, for example, magnesium stearate, sucrose fatty acid ester, polyethylene glycol, talc, stearic acid and the like are exemplified. Use of polyethylene glycol as the lubricant provides the stable solid preparation of which the decomposition over time of the pharmaceutical ingredient is controlled. At that time, polyethylene glycol is used in an amount of, for example, 0.01 to 10 parts by weight, preferably 0.1 to 5 parts by weight, per 100 parts by weight of the solid preparation.

As the colorants, for example, various food colorants such as Food Yellow No. 5, Food Red No.2, Food Blue No. 2 and the like; food lakes, red iron oxide and the like are exemplified.

As the stabilizers, for example, a basic substance in the case of the basic

pharmaceutical ingredient and an acidic substance in the case of the acidic pharmaceutical ingredient are exemplified.

[0020]

As the disintegrators, for example, disintegrators called super disintegrators such as crospovidone [manufactured by ISP Inc. (U.S.A.), BASF (Germany)], croscarmellose sodium [FMC-Asahi Chemical Industry Co., Ltd.], carmellose calcium [Gotoku Chemical (Yakuhin)]; hydroxypropylcellulose; carboxymethylstarch sodium [Matsutani Chemical Co., Ltd.]; corn starch and the like are exemplified. Among others, crospovidone is preferably used. Such two or more disintegrators are optionally used in an admixture thereof with suitable ratio.

As crospovidone, any cross-linked homopolymer such as 1-ethenyl-2-pyrrolidinone homopolymer may be used, and usually crospovidone having a molecular weight of at least 1,000,000 is used. As crospovidone which is commercially available, for example, Cross-linked povidone, Kollidone CL [manufactured by BASF (Germany)], Polyplasdone XL, Polyplasdone XL-10, INF-10 [manufactured by ISP Inc. (U.S.A.)], polyvinylpolypyrrolidone, PVPP, 1-vinyl-2-pyrrolidinone homopolymer and the like are concretely exemplified.

Such disintegrator is used in an amount of, for example, 0.1 to 20 parts by weight, preferably 1 to 10 parts by weight, per 100 parts by weight of the solid preparation.

[0021]

In case that the pharmaceutical ingredient is an acid-labile pharmaceutical ingredient such as lansoprazole, omeprazole, rabeprazole, pantoprazole and the like, a basic inorganic salt is preferably incorporated to stabilize the pharmaceutical ingredient in the pharmaceutical preparation. As the basic inorganic salt, a basic inorganic salt of

sodium, potassium, magnesium and/or calcium are/is exemplified. Two or more of these basic inorganic ingredients are optionally used in an admixture with suitable ratio.

As the basic inorganic salt of sodium, for example, sodium carbonate, sodium hydrogencarbonate and the like are exemplified.

As the basic inorganic salt of potassium, for example, potassium carbonate, potassium hydrogencarbonate, potassium sodium carbonate and the like exemplified.

As the basic inorganic salt of magnesium, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16} \cdot CO_3 \cdot 4H_2O$] and aluminum magnesium hydroxide [$2.5MgO \cdot Al_2O_3 \cdot xH_2O$] are exemplified. Among others, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide and the like are preferable.

As the basic inorganic salt of calcium, for example, precipitated calcium carbonate, calcium hydroxide and the like are exemplified.

Such basic inorganic salt is preferably the basic inorganic salt of magnesium, more preferably heavy magnesium carbonate, magnesium carbonate, magnesium oxide and magnesium hydroxide.

The amount of the basic inorganic salt to be used can be appropriately selected depending on the kind of the basic inorganic salt and is, for example, about 0.3 to 200 % by weight, preferably about 1 to 100 % by weight, more preferably about 10 to 50 % by weight, especially preferably about 20 to 40 % by weight relative to the pharmaceutical ingredient.

[0022]

The rapidly disintegrable solid preparation of the present invention can be

produced in accordance with a conventional method in the field of pharmaceutical preparation. As such method, for example, a method comprising blending the pharmaceutical ingredient, the sugar and the low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group after adding water in need, molding, and then drying in need is exemplified. However, the rapidly disintegrable solid preparation of the present invention can be produced also without water.

The blending procedure can be carried out by any conventional blending techniques such as admixing, kneading, granulating and the like. The blending procedure is carried out by using an apparatus such as Vertical Granulator VG10 [manufactured by Powrex Corp.], Universal Kneader [manufactured by Hata Iron Works Co., Ltd.], fluidized bed granulator LAB-1 and FD-3S [manufactured by Powrex Corp.], centrifugal fluidized coating granulator MP-10, MP-400 [manufactured by Powrex Corp.] and the like.

The molding procedure can be carried out by tabletting with pressure of 0.5 to 3 ton/cm^2 by using, for example, a single-punch tabletting machine [manufactured by Kikusui Seisakusho], a rotary type tabletting machine [manufactured by Kikusui Seisakusho] and the like when the rapidly disintegrable solid preparation is a tablet.

The drying procedure can be carried out by any techniques such as vacuum drying, fluidized-bed drying and the like used to dry the general pharmaceutical preparation.

[0023]

The rapidly disintegrable solid preparation of the present invention thus obtained exhibits fast disintegrability or dissolubility in the oral cavity, and suitable strength of the preparation. Further the rapidly disintegrable solid preparation of the

present invention is improved in chalky taste and has no roughness.

The orally disintegration time of the rapidly disintegrable solid preparation of the present invention (the time for healthy male or female adults to complete disintegration by buccal saliva) is usually about 5 to about 50 seconds, preferably about 5 to about 40 seconds, more preferably about 5 to about 35 seconds.

The strength of the rapidly disintegrable solid preparation of the present invention (measurement with a tablet hardness tester) is usually about 2 to about 20 kg, preferably about 4 to about 15 kg.

[0024]

The rapidly disintegrable solid preparation of the present invention can be safely administered orally to mammals such as mouse, rat, rabbit, cat, dog, bovine, horse, monkey, human and the like.

While the dosage amount of the rapidly disintegrable solid preparation varies depending on a pharmaceutical ingredient, a subject, a kind of disease and the like, the dosage amount is selected so that the dosage amount of the pharmaceutical ingredient can be an effective amount.

For instance, when lansoprazole is used as the pharmaceutical ingredient, the rapidly disintegrable solid preparation of the present invention is useful for treatment and prevention of digestive ulcer (such as gastric ulcer, duodenal ulcer, anastomic ulcer, Zollinger-Ellison syndrome), gastritis, reflex esophagitis and the like; eradication of H. pylori; suppression of upper gastrointestinal bleeding caused by digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal bleeding caused by invasive stress (such as stress caused by a large-scale operation necessitating the following intensive management or cerebrovascular disease, head injury, failure of many organs, burn injury of a wide range which necessitate intensive care); treatment

and prevention of ulcer caused by non-steroidal anti-inflammatory agent; treatment and prevention of gastric hyperacidity and ulcer caused by postoperative stress; administration before anesthesia and the like. The dosage amount of the preparation per an adult (body weight: 60 kg) is 0.5 to 1500 mg/day, preferably 5 to 150 mg/day, as lansoprazole.

[0025]

When voglibose is used as the pharmaceutical ingredient, the rapidly disintegrable solid preparation of the present invention is useful for treatment and prevention of obesity, adiposis, lipemia, diabetes mellitus and the like. The dosage amount of the preparation per an adult (body weight: 60 kg) is 0.01 to 30 mg/day, preferably 0.1 to 3 mg/day, as voglibose. The rapidly disintegrable solid preparation can be administered once a day, or 2 to 3 times separately a day.

When manidipine hydrochloride is used as the pharmaceutical ingredient, the rapidly disintegrable solid preparation of the present invention is useful for treatment and prevention of circulatory system diseases such as hypertension, ischemic heart disease (e.g., angina pectori, myocardial infarction and the like), cerebral and peripheral circulatory disorders (e.g., cerebral infarction, transient ischemic attack, constriction of renal artery and the like) and the like. The dosage amount of the preparation per an adult (body weight: 60 kg) is about 1 to 200 mg/day, preferably 10 to 20 mg/day, as manidipine hydrochloride. The rapidly disintegrable solid preparation is usually administered orally once a day after breakfast.

Further, when candesartan cilexetil is used as the pharmaceutical ingredient, the rapidly disintegrable solid preparation of the present invention is useful for treatment and prevention of hypertension, heart diseases, cerebral apoplexy, renal diseases and the like. The dosage amount of the preparation per an adult (body weight: 60 kg) is 1 to 50

mg/day, preferably 2 to 30 mg/day, as candesartan cilexetil.

[0026]

[Best Mode for Carrying out the Invention]

The present invention is more specifically explained by means of the following Reference Examples, Examples and Test Examples. It is to be understood that the present invention is not limited to these Examples.

Unless otherwise specifically indicated, the following "%" means % by weight.

Also, the content of hydroxypropoxyl group is measured in accordance with the methods described in Japanese Pharmacopoeia (e.g., 13th edition). The physical properties (hardness and disintegration time) of the tablets were determined by the following test methods.

(1) Hardness test

Determination was carried out with a tablet hardness tester [manufactured by Toyama Sangyo Co. Ltd.]. The test was performed in 10 runs and mean values were shown.

(2) Oral disintegration time

Time for complete disintegration or dissolution of the tablets only by saliva in the oral cavity was determined.

[0027]

[Examples]

Reference Example 1

An alkaline cellulose comprising 24.1 % of NaOH, 1.7 % of Na_2CO_3, 42.9 % of cellulose, 31.8 % of H_2O was obtained by immersing wood pulp in 49% aqueous solution of sodium hydroxide and then by pressing it. A reactor was charged with 100 parts by weight of the alkaline cellulose. Then, nitrogen gas replacement was carried

out. After the replacement, 5 parts by weight of propylene oxide was charged in the reactor and reacted with stirring at 40°C for 1 hour, at 50°C for 1 hour and at 70°C for 1 hour to provide 103 parts by weight of a reactant.

On the other hand, a kneader was charged with 2.5 parts by weight of hot water at 65°C and 0.13 parts by weight of glacial acetic acid (about 40 % by weight against equivalent for neutralization, initial neutralized acid) and therein, 1 part by weight of the above resulting alkaline cellulose was dispersed. Then, the temperature was adjusted at 30°C to dissolve a part of the reactant, and 0.20 part by weight of glacial acetic acid (remain of equivalent for neutralization, complete neutralized acid) to provide a processed fiber product containing a part of dissolution and a part of deposit.

The resulting product was washed with hot water at about 80°C, drained, dried, ground by means of high rolling impact grinder, and sifted by means of a 100 mesh sieve to provide the powder of low-substituted hydroxypropylcellulose LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm).

Reference Example 2

Powders of low-substituted hydroxypropylcellulose LH-23 (content of hydroxypropyl group: 5.7 % by weight, average particle diameter: 30.8 μm) were obtained in the same manner as in Reference Example 1.

[0028]

Example 1

(1) Production of powders having a core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp., MP-10] was charged with 900 g of Nonpareil 105 (trade name) (particle diameter: 100 to 200 μm). While the inlet air temperature and the outlet air temperature were controlled at 70°C and about 30°C respectively, the Nonpareil was coated by spraying a

spray liquid of the following composition prepared in advance in accordance with the tangential spray method at the spray rate of 22 g/min. Then, drying was carried out for 10 minutes. The resulting granules were sieved through a #60 circular sieve (250 μm) and a #100 circular sieve (150 μm) to provide 2186 g of powders (150 to 250 μm) having a core.

[Spray liquid]

Lansoprazole	927 g
Magnesium carbonate	309 g
Low-substituted hydroxypropylcellulose LH-32	154.5 g
(Content of hydroxypropyl group: 8.8 % by weight)	
(Average particle diameter: 17.57 μm)	
Hydroxypropylcellulose (Type SSL)	309 g
Purified water	3955 g

(2) Production of film-undercoated powders having a core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp., MP-10] was charged with 2040 g of the above powders having a core. While the inlet air temperature and the outlet air temperature were controlled at 75°C and about 40°C respectively, an undercoating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at the spray rate of 13 g/min. 2145 g of film-undercoated powders having a core was obtained.

[Undercoating liquid]

Hydroxypropylmethylcellulose	264 g
(Type 2910, viscosity: 3 centistokes)	
Purified water	5016 g

[0029]

(3) Production of enteric-coated powders having a core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp., MP-10] was charged with 1710 g of the above film-undercoated powders having a core.

While the inlet air temperature and the outlet air temperature were controlled at 70°C and about 40°C respectively, an enteric film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at the spray rate of 19 g/min. Then, drying was carried out for 7 minutes. The resulting granules were sieved through a #42 circular sieve (355 μm) and a #80 circular sieve (177 μm) to provide 2393 g of powders (177 to 355 μm) having a core.

[Enteric film coating liquid]

Eudragit L30D-55	5016.4 g
Eudragit NE30D	559.0 g
Triethyl citrate	333.7 g
Glyceryl monostearate	106.5 g
Polysorbate 80	34.8 g
Red iron oxide	1.8 g
Purified water	2547.1 g

[0030]

(4) Production of mannitol-overcoated enteric-coated powders having a core

A centrifugal fluidized coating granulator [manufactured by Powrex Corp., MP-10] was charged with 600 g of the above enteric-coated powders having a core. While the inlet air temperature and the outlet air temperature were controlled at 65°C and about 32°C respectively, a film coating liquid of the following composition prepared in advance was sprayed in accordance with the tangential spray method at the spray rate of 11 g/min. Then, drying was carried out for 7 minutes. 617 g of overcoated enteric-coated powders having a core was obtained.

[Film coating liquid]

Mannitol	33 g
Purified water	297 g

(5) Production of mannitol granulated powders

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 800 g of mannitol [manufactured by Merck Japan Co., Ltd.], and granulation was carried out while spraying 315 g of purified water. The granules were dried to provide 727.3 g of granulated powders.

[0031]

(6) Production of mixed powders

To 105 g of the above overcoated enteric-coated powders having a core were added 97.3 g of the above mannitol-granulated powders, 15.0 g of low-substituted hydroxypropyl cellulose LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm), 22.5 g of crystalline cellulose [CEOLUS KG-801 (trade name), manufactured by Asahi Chemical Industry Co., Ltd.], 7.5 g of crospovidone, 1.5 g of anhydrous citric acid, 0.45 g of aspartame and 0.75 g of magnesium stearate, which were admixed in a bag to give mixed powders.

(7) Production of orally disintegrable tablets

250 g of the above mixed powder was tabletted by a pounder (15R, 11 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.5 ton/cm^2 to provide tablets each weighing 500 mg.

The hardness and oral disintegration time of each tablet thus obtained were 5.9 kg and 30 seconds respectively.

[0032]

Example 2

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 0.6 g of voglibose, 410.4 g of erythritol [manufactured by Nikken Chemicals Co., Ltd.], 120.0 g of low-substituted hydroxypropylcellulose LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm), 30.0 g of CEOLUS KG-801 [manufactured by Asahi Chemical Industry Co., Ltd.], 30 g of crospovidone, 6.0 g of anhydrous citric acid and 1.2 g of aspartame, and granulation was carried out while spraying purified water. After drying, 1.8 g of magnesium stearate was incorporated. The resulting powder was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 300 mg.

The hardness and oral disintegration time of each tablet thus obtained were 10.7 kg and 26 seconds respectively.

[0033]

Example 3

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 0.6 g of voglibose, 440.4 g of erythritol [manufactured by Nikken Chemicals Co., Ltd.], 120.0 g of low-substituted hydroxypropylcellulose LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm), 30.0 g of crospovidone, 6.0 g of anhydrous citric acid and 1.2 g of aspartame, and granulation was carried out while spraying purified water. After drying, 1.8 g of magnesium stearate was incorporated. The resulting powder was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 300 mg.

The hardness and oral disintegration time of each tablet thus obtained were 7.1 kg and 20 seconds respectively.

[0034]

Example 4

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 0.4 g of voglibose, 470.6 g of erythritol [manufactured by Nikken Chemicals Co., Ltd.], 120.0 g of low-substituted hydroxypropylcellulose LH-33 (content of hydroxypropoxyl group: 5.7 % by weight, average particle diameter: 30.8 μm), 6.0 g of anhydrous citric acid and 1.2 g of aspartame, and granulation was carried out while spraying purified water. After drying, 1.8 g of magnesium stearate was incorporated. The resulting powders was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.25 ton/cm^2 to provide tablets each weighing 300 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.5 kg and 23 seconds respectively.

[0035]

Example 5

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 0.4 g of voglibose, 470.6 g of mannitol [manufactured by Merck Japan Co., Ltd.], 120.0 g of low-substituted hydroxypropylcellulose LH-23 (content of hydroxypropoxyl group: 5.7 % by weight, average particle diameter: 30.8 μm), 6.0 g of anhydrous citric acid and 1.2 g of aspartame, and granulation was carried out while spraying purified water. After drying, 1.8 g of magnesium stearate was incorporated. The resulting powder was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.25 ton/cm^2 to provide tablets each weighing 300 mg.

The hardness and oral disintegration time of each tablet thus obtained were 4.3

kg and 27 seconds respectively.

[0036]

Example 6

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 40.0 g of manidipine hydrochloride, 460.94 g of erythritol [manufactured by Nikken Chemicals Co., Ltd.], 60.0 g of low-substituted hydroxypropylcellulose LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm), 30.0 g of crospovidone, 6.0 g of anhydrous citric acid and 1.2 g of aspartame, and granulation was carried out while spraying purified water in which was dissolved 0.06 g of yellow iron oxide. After drying, 1.8 g of magnesium stearate was incorporated. The resulting powder was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.0 ton/cm^2 to provide tablets each weighing 300 mg.

The hardness and oral disintegration time of each tablet thus obtained were 6.0 kg and 21 seconds respectively.

[0037]

Test Example 1

Low-substituted hydroxypropylcellulose LH-30 (content of hydroxypropoxyl group: 14.6 % by weight, average particle diameter: 17.26 μm), LH-31 (content of hydroxypropoxyl group: 11.0 % by weight, average particle diameter: 18.18 μm), LH-32 (content of hydroxypropoxyl group: 8.8 % by weight, average particle diameter: 17.57 μm) and LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm) were administered to 4 females respectively, and dissolubility and taste were evaluated.

The results are shown in [Table 1].

[Table 1]

Low-substituted hydroxypropylcellulose	Trial subject	Evaluation
LH-30	4/4	difficult of dissolution in the oral cavity
LH-31	4/4	dissolved in the oral cavity, chalky taste
LH-32	4/4	dissolved in the oral cavity, chalky taste
LH-33	4/4	dissolved in the oral cavity, no chalky taste

As shown in [Table 1], dissolubility and chalky taste are improved, and further no roughness was felt, with respect to the case of low-substituted hydroxypropylcellulose LH-33 comprising 5.8 % by weight of hydroxypropoxyl group.

[0038]

Test Example 2

Tablets were produced by using low-substituted hydroxypropylcellulose LH-30 (content of hydroxypropoxyl group: 14.6 % by weight, average particle diameter: 17.26 μm), LH-31 (content of hydroxypropoxyl group: 11.0 % by weight, average particle diameter: 18.18 μm), LH-32 (content of hydroxypropoxyl group: 8.8 % by weight, average particle diameter: 17.57 μm) and LH-33 (content of hydroxypropoxyl group: 5.8 % by weight, average particle diameter: 17.8 μm) in accordance with the following manner.

A fluidized bed granulator [manufactured by Powrex Corp., LAB-1] was charged with 398.5 g of erythritol [manufactured by Nikken Chemicals Co., Ltd.] and 100 g of low-substituted hydroxypropylcellulose, and granulation was carried out while spraying purified water. After drying, 1.5 g of magnesium stearate was incorporated. The resulting powder was tabletted by a pounder (beveled edge, 10 mm in diameter) using a rotary type tabletting machine at the tabletting pressure of 1.0 ton/cm^2 to provide

tablets each weighing 300 mg.

The resulting tablets were administered to 4 females respectively, and dissolubility and taste was evaluated.

The results are shown in [Table 2].

[Table 2]

Low-substituted hydroxypropylcellulose	Trial subject	Evaluation
LH-30	4/4	not dissolved in the oral cavity
LH-31	4/4	not dissolved in the oral cavity
LH-32	4/4	felt adhesiveness in the oral cavity, still chalky taste after dissolution
LH-33	4/4	fast dissolved in the oral cavity, a little chalky taste

As shown in [Table 2], dissolubility and chalky taste are improved, and further no roughness was felt, with respect to the case of low-substituted hydroxypropylcellulose LH-33 comprising 5.8 % by weight of hydroxypropoxyl group.

[0039]

[Effect of the Invention]

The rapidly disintegrable solid preparation of the present invention is usable for treatment and prevention of various kinds of diseases as the rapidly disintegrable solid preparation, especially as the oral rapidly disintegrable solid preparation, which can be administered to elders or children without water because the preparation has superior disintegrability and dissolubility.

And, the rapidly disintegrable solid preparation has superior long-term stability because the preparation has suitable strength.

Further, the rapidly disintegrable solid preparation of the present invention is

improved in dissolubility and chalky taste, and has no roughness.

[Document Name] Abstract

[Abstract]

[Problem] To provide a rapidly disintegrable solid preparation having fast disintegrability, suitable strength and no roughness.

[Means to solve the problem] A rapidly disintegrable solid preparation which comprises (i) a pharmaceutical ingredient, (ii) a sugar and (iii) a low-substituted hydroxypropylcellulose having 5 % by weight or more to less than 7 % by weight of hydroxypropoxyl group.

[Selected Drawings] None